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Antioxidants – Good for Your Health, Good For Your Hearing

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If you've been diligently working in hearing conservation for a few years, you probably have your customary way of describing the biological effects of noise on the hearing system, based on what you were originally taught. Traditionally, we have used ominous words like "permanent", "irreparable" and "irreversible" to try to convince skeptical workers that they ought to heed our recommendations for hearing conservation practices. As Occupational Hearing Conservationists (OHCs), you've had your work cut out for you…especially if determined workers doubt your point of view or training. One day, one of these workers might even say, "Hey, I read that they have some medicine now that can prevent harmful effects of noise on the ear." Although such a remedy is not available now from your pharmacy, you should know that there have been some landmark discoveries in auditory research about how the cochlea is injured during excessive noise exposure and how it may sometime be possible to reverse or prevent acute noise damage with medications. This article will summarize some of this research and recommend further reading for OHCs who may be interested in this fast-paced research activity.

When the cochlea is exposed to loud noise, damage occurs that can be classified as either mechanical (e.g., tearing apart the delicate tissue structures when loud blasts occur above 125 - 130 dB SPL) or metabolic exhaustion (far less traumatic, but more common, habitual noise exposures). Metabolic exhaustion occurs when toxic waste products known as **free radicals** or **reactive oxygen species** (**ROS**) are formed after the cells in the cochlea are stressed by reductions in cochlear blood flow, excessive and toxic levels of neurotransmitters like glutamate, changes in calcium balances in the cell, and other stress-related changes that are induced by noise. These free radicals, or ROS, injure a wide variety of critical structures in the cochlea, causing cell damage and cell death that are the effects we classically illustrate in our hearing conservation lectures. What's new to the picture, though, is the idea that our body can react to a brutal stress like noise trauma by presenting a defense of **antioxidant** enzymes and other molecules. **Figure 1** shows a sequence of events that depict how the cochlea's stress can ultimately cause its death, summarizing studies from several labs [see Kopke, 2002].

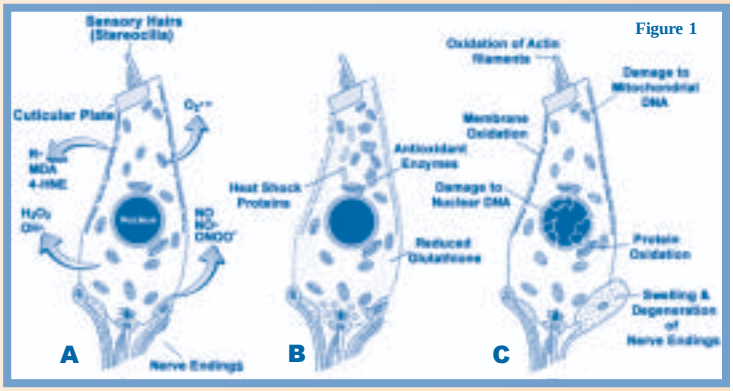

Figure 1: **Noise-Induced Oxidative Cochlear Injury.** ***A:*** Four main forms of reactive oxygen species (ROS) produced by hair cells undergoing oxidative stress. Acoustic trauma causes the stereocilia to prompt the hair cell to generate ROS, which can kill the cell. ***B:*** Main antioxidant defenses available to a hair cell that may control oxidative damage from ROS (see text). These defense mechanisms work by directly blocking the creation of ROS or by removing the ROS from the cell before it can damage the nucleus or other important cellular structures. ***C:*** Forms of cell damage and injury caused by ROS when the damage exceeds capability of antioxidant defenses. These forms of cell damage and injury often result in cell death.

Figure 1A shows how over stimulation of the hair cell prompts excessive generation of free radicals (indicated by their chemical abbreviations). In response, cochlear defenses take place [like production of antioxidant enzymes, antioxidant molecules or production of glutathione (GSH), and other factors (as shown in **Figure 1B**)]. Finally, when these antioxidant defenses are overwhelmed, the hair cell is subject to serious damage to its nuclear DNA, mitochondria, and membranes (as depicted in **Figure 1C**). When hair cells are damaged in this way, they are prone to a genetically programmed cell death sequence (known as **apoptosis**), in which the ongoing

continued on page 9

Content

Antioxidants

continued from page 1

loss of hair cells can continue for days to weeks after an acute noise insult. In summary, excessive noise stresses the cell, generating some defenses (that may help), but can cause cell death (when overwhelmed).

The "new" perspectives of auditory research, however, indicate that permanent noise-related hearing loss can be reduced with increases in defenses provided by inner-ear antioxidant enzyme activity, inner-ear GSH, or the administering of antioxidant compounds [see Ohinata (2000), Hu et al, (1997), and Henderson et al. (1999)]. In addition, the ear's vulnerability to noise and toxins in the basal region of the cochlea (known to be critical for high-frequency hearing sensitivity) may be due to a relative weakness of antioxidant defenses (i.e., reduced GSH) in that region (Sha et al., 2001). Research has suggested that GSH is probably the key inner ear antioxidant defense molecule, in both preventing and treating acute noise-induced hearing loss (Kopke et al., 2000, Kopke et al., 2002). GSH is not well absorbed into cells and is degraded by the liver. Therefore, strategies to increase inner-ear GSH levels have been tested using a variety of drugs, which have been already approved by the FDA for other applications. N-acetylcysteine (NAC) and methionine (MET) are two such agents that can be used by the ear to synthesize GSH. NAC can counter the harmful effects of noise on the cochlea by acting as a free radical scavenger and by replenishing GSH. The replenished GSH also detoxifies free radicals, reduces the effects of excessive and toxic effects of glutamate and inhibits programmed cell death.

One of the promising outcomes of basic research has been the indication that NAC and related compounds may greatly reduce noise-induced cochlear hair cell loss, as well as permanent hearing loss, if administered prior to the noise and then for a short period of time after the exposure (Kopke et al., 2000, Kopke et al., 2002). **Figure 2** displays a dramatic reduction in permanent hearing loss achieved when NAC is administered prior to continuous or impulsive noise exposures. In addition, if NAC and related compounds are given shortly after an acute noise injury, research has indicated reduced permanent hearing loss as well.

Since this basic research has been promising in animal studies, the next step in the development of this technology is to perform well-designed human clinical trials in occupational settings where some hearing loss occurs despite the appropriate use of hearing protection devices. Once clinical efficacy is established there are a number of clinical and occupational scenarios where the technology could be employed. For example, in very noise-intensive occupational environments, workers could take NAC during their work shifts in addition to wearing their hearing protection devices. In some military situations (like aircraft carriers), noise levels exceed attenuation capabilities of hearing protection devices and sailors may benefit from use of pharmacological technology. In addition, if we could identify those who are susceptible to noise damage, they might well benefit from such treatments with pharmacological agents. Lastly, since NAC and related agents appear to be effective even if given shortly after a loud noise exposure, those with noise-induced tinnitus could take the medication soon after the insult with a reduction in permanent hearing loss anticipated.

Figure 2

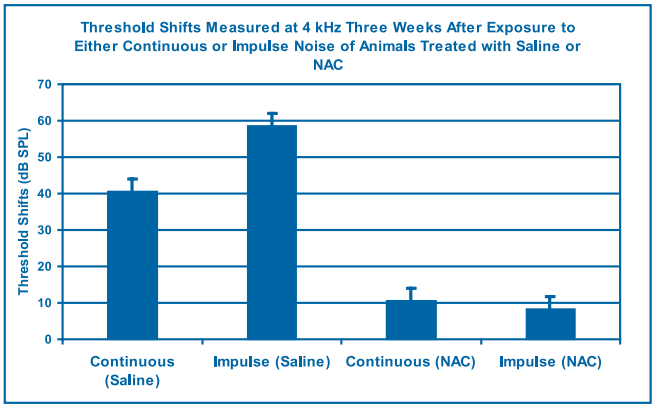

Figure 2: The Effects of Noise on Hearing Thresholds. *Three-week post-noise hearing threshold shifts measured on chinchillas (pre-treated with either saline or NAC) after continuous or impulsive noise exposures. Threshold shifts were measured by auditory brainstem response (ABR) at 4 kHz. Post-noise ABRs were compared to baseline, pre-noise exposure ABRs. The threshold shifts after each of the noise exposures was significantly lower for the NAC-treated animals compared to noise-exposed, saline-treated animals. Continuous noise was an octave band noise centered at 4 kHz, delivered at 105 dB SPL for 6 hrs. Impulse noise was composed of 75 pairs of impulses at 150 dB SPL given at a rate of two per second.*

While engineering and personal hearing protection devices have been, and will continue to be mainstays of noise-induced hearing loss prevention, there is much anticipation that antioxidant molecules may play an important adjunctive role in hearing conservation practices in the future. To keep your hearing conservation training up to date, continue looking for more information about pharmacological noise research in this publication and in the scientific literature.

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